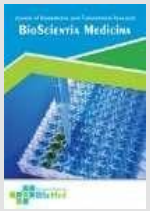
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

The Gut-Muscle Axis in Sarcopenia: A Meta-Analysis of Gut Microbiome Compositional Features and Their Correlation with Muscle Mass, Strength, and Physical Performance in Older Adults

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ARTICLE INFO

Keywords:
Dysbiosis
Gut microbiome
Gut-muscle axis
Older adults
Sarcopenia

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v9i9.1384

A B S T R A C T

Background: Sarcopenia, the age-related decline in muscle mass and function, is a major geriatric syndrome. The gut-muscle axis has emerged as a key area of investigation, yet the association between gut microbiome composition and sarcopenic parameters in humans remains quantified by a collection of studies with varied methodologies. This meta-analysis aimed to synthesize the existing correlational evidence linking gut microbiome features to the core components of sarcopenia in older adults. **Methods:** We performed a systematic search of PubMed, Scopus, Web of Science, and Embase for observational studies published between January 2015 and July 2025 that assessed gut microbiome composition and sarcopenia metrics in adults aged ≥60. Correlation coefficients (r) were pooled using a random-effects model. We assessed heterogeneity using the I^2 statistic, conducted pre-specified subgroup and sensitivity analyses, and evaluated study quality with the Newcastle-Ottawa Scale (NOS). **Results:** Six cross-sectional studies (N=1,189) met the inclusion criteria. The methodological quality was high (median NOS score = 8). The pooled analysis revealed a significant, small positive correlation between gut microbial alpha diversity and muscle strength (handgrip strength) (pooled r = 0.19, 95% CI: 0.11-0.27; I^2 = 41%). The relative abundance of the genus *Faecalibacterium*, known for its potential to produce butyrate, was significantly correlated with physical performance (pooled r = 0.24, 95% CI: 0.16-0.32; I^2 = 28%). A non-significant negative correlation was found between the family *Enterobacteriaceae* and muscle mass (pooled r = -0.14, 95% CI: -0.29-0.01; I^2 = 62%). Subgroup analysis suggested this heterogeneity was partly explained by the diagnostic criteria used for sarcopenia. **Conclusion:** This meta-analysis provides quantitative evidence of a modest but significant association between gut microbiome composition and muscle health in older adults. A microbial profile with higher diversity and greater abundance of putative beneficial taxa is correlated with better muscle function. These associative findings, while limited by the cross-sectional nature of the data and the potential for reverse causality, reinforce the clinical relevance of the gut-muscle axis and underscore the need for longitudinal, multi-omic studies to elucidate mechanisms and test microbiome-targeted therapies.

1. Introduction

The global population is undergoing a profound demographic transformation.[1] According to the World Health Organization (WHO), the number of individuals aged 65 and over, which stood at 703 million in 2019, is on a trajectory to reach 1.5 billion by 2050.[2] This demographic shift, while a testament to public health successes, brings to the forefront the challenge of managing age-associated chronic diseases and geriatric syndromes. Among these, sarcopenia has been identified as a paramount public health concern, contributing significantly to frailty, morbidity, and

loss of autonomy in later life. Sarcopenia, from the Greek *sarx* (flesh) and *penia* (loss), is a progressive skeletal muscle disorder characterized by the loss of muscle mass combined with a decline in muscle strength and/or physical performance.[3] Its prevalence escalates with age, impacting approximately 5-13% of adults in their 60s and as many as 50% of those over 80. The clinical consequences are severe, creating a cascade of adverse outcomes including an elevated risk of falls and fractures, functional decline, increased frequency and duration of hospitalizations, and a marked increase in all-cause mortality.[4] This places a formidable strain not only on the affected individuals and their families but also on global healthcare economies.

The pathophysiology of sarcopenia is a complex web of interacting biological processes.[5] The homeostatic balance between muscle protein synthesis and degradation is disrupted by a confluence of factors, including anabolic resistance, where muscle tissue responds less efficiently to stimuli like amino acids and exercise.[6] Key mechanisms include a state of chronic, low-grade systemic inflammation, often called "inflammaging"; increased oxidative stress damaging cellular components; and a decline in mitochondrial number and function, leading to an energy deficit within muscle cells. These are compounded by age-related changes in the endocrine milieu, including reduced levels of anabolic hormones like testosterone and growth hormone. The cumulative effect is a net loss of muscle fibers, particularly the powerful type II fibers, and an infiltration of adipose and fibrous tissue into the muscle, a condition known as myosteatosis, which further degrades muscle quality and function.[6] In parallel with our deepening understanding of muscle aging, a paradigm shift has occurred in biomedical science, recognizing the gut microbiome as a central regulator of human health and disease. The human gut harbors a dense and diverse ecosystem of trillions of microorganisms, whose collective genome, the microbiome, vastly outnumbers our own.[7] This microbial community is now understood to be a critical metabolic organ, indispensable for nutrient metabolism, vitamin synthesis, drug metabolism, immune system education, and defense against pathogens. The composition of this community is dynamic, shaped by genetics, diet, lifestyle, and medications, and it undergoes significant changes across the lifespan.[7] A common feature of aging is a shift towards a "dysbiotic" state, characterized by reduced microbial diversity, a depletion of beneficial commensal bacteria, and an expansion of pro-inflammatory pathobionts.[8] This dysbiosis has been robustly associated with numerous age-related conditions.

The confluence of these two fields of research—geriatric muscle biology and microbiology—has given rise to the concept of the "gut-muscle axis." This model posits a bidirectional communication network between the gut and skeletal muscle, mediated by microbial, endocrine, immune, and neural signals.[8] Several pathways are hypothesized to underpin this axis. First, dysbiosis can compromise the integrity of the intestinal barrier, leading to "leaky gut" and the translocation of bacterial components like lipopolysaccharide (LPS) into the bloodstream. This "metabolic endotoxemia" activates systemic inflammation via Toll-like receptor 4 (TLR4) signaling, promoting a catabolic state in muscle. Second, the gut microbiota ferments indigestible dietary fibers into beneficial metabolites, chief among them being short-chain fatty acids (SCFAs) like butyrate. SCFAs are not just fuel for colonocytes; they act systemically as signaling molecules through G-protein coupled receptors (GPR41, GPR43) and as epigenetic modulators (histone deacetylase inhibitors), exerting anti-inflammatory effects and potentially enhancing muscle mitochondrial biogenesis via pathways like PGC-1α. Third, the microbiome influences the bioavailability and metabolism of essential nutrients for muscle, including branch-chain amino acids (BCAAs).

However, it is crucial to distinguish between microbial composition and function. Much of the human research in this area, including the studies

synthesized in this review, has relied on 16S ribosomal RNA (rRNA) gene sequencing. This technique provides a taxonomic census of the bacterial community—it tells us "who is there." It does not, however, directly measure the functional output of that community. Therefore, when a study reports a lower abundance of the genus *Faecalibacterium*, the conclusion of reduced butyrate production is a reasonable but unconfirmed inference. The actual metabolic activity of the microbiome can only be definitively assessed through methods like shotgun metagenomics (which reveals functional gene potential) and metabolomics (which measures the actual metabolites present).[9] This composition-function gap is a fundamental challenge in the field and a key interpretative lens for this meta-analysis. Furthermore, the clinical construct of sarcopenia itself is heterogeneous. While this review focuses on community-dwelling older adults to reduce confounding, sarcopenia within this group can be primary (driven primarily by the aging process) or secondary to chronic diseases that are common in later life. The underlying drivers of muscle loss and the associated microbial signatures may differ between an otherwise healthy 80-year-old and one with stable chronic heart failure.[10] Current observational studies rarely stratify by sarcopenia etiology, meaning that analyses of the gut-muscle axis are likely examining a mix of potentially distinct clinical phenotypes. Despite these complexities, a growing number of observational studies have reported associations between specific microbial features and sarcopenic parameters. While compelling, these studies are often limited by small sample sizes and methodological variability. A quantitative synthesis of this evidence is needed to establish the overall magnitude and consistency of these associations.[10]

While narrative reviews have extensively discussed the gut-muscle axis, and a prior systematic review has cataloged the findings, a quantitative meta-analysis of the correlational data linking microbial features to all three clinical components of sarcopenia (mass, strength, and performance) has not been performed. After a thorough search of the PROSPERO database and current literature, we confirm that this study represents the first attempt to pool these specific effect sizes. By doing so, this research moves beyond qualitative description to provide a more precise, generalizable, and critically appraised understanding of the associative relationship between the gut microbiome and muscle health in older humans. The primary aim of this study was to conduct a systematic review and meta-analysis to determine the magnitude and direction of the association between gut microbiome compositional features (specifically, alpha diversity and the relative abundance of key taxa) and quantitative measures of skeletal muscle mass, muscle strength, and physical performance in community-dwelling adults aged 60 years and above.

2. Methods

This systematic review and meta-analysis were designed, conducted, and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. A comprehensive literature search was executed across four major electronic databases: PubMed/MEDLINE, Scopus, Web of Science, and Embase, for articles published from January 1st, 2015, to July 1st, 2025. The search strategy was designed to be sensitive, combining MeSH terms and free-text keywords covering three domains: population, exposure, and outcome. In brief, the search combined terms such as (sarcopenia OR muscle atrophy OR handgrip strength OR gait speed) AND (gut microbiota OR microbiome OR dysbiosis OR 16S rRNA) AND (elderly OR older adults OR aged). The search was restricted to studies published in the English language. To ensure comprehensiveness, the reference lists of all included articles and relevant narrative reviews were manually scanned for additional eligible studies.

Studies were deemed eligible for inclusion if they met all the following criteria: Study Design: Observational (cross-sectional, case-control, or cohort designs); Population: Community-dwelling human participants with a mean or median age of 60 years or older. We excluded studies focused exclusively on

hospitalized patients or residents of long-term care facilities to minimize the profound confounding effects of acute illness, immobility, and institutional diets on the microbiome; Exposure: Assessment of gut microbiome composition from fecal samples using high-throughput sequencing (16S rRNA or shotgun metagenomics); Outcomes: Reporting of at least one quantitative measure of sarcopenia, defined as: Muscle Mass: Assessed by a validated body composition technique, primarily dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA); Muscle Strength: Assessed by handgrip dynamometry (HGS); Physical Performance: Assessed by validated functional tests, including gait speed, the Short Physical Performance Battery (SPPB), or the Timed Up and Go (TUG) test; Data Availability: Provided a statistical measure of association, specifically a correlation coefficient (Pearson's r or Spearman's ρ), between a defined microbial feature and a sarcopenia outcome, or presented sufficient data to allow for the calculation of such a coefficient.

All retrieved citations were managed using EndNote X9. After automated duplicate removal, two reviewers independently screened titles and abstracts. Full texts of potentially relevant articles were then retrieved and independently assessed for final eligibility by the same two reviewers. Any conflicts were resolved through consensus discussion, with adjudication by a third senior reviewer if necessary. A standardized data extraction template was used by the two reviewers to independently extract data. Information collected included: (1) study identifiers (author, year, country); (2) study design and sample size; (3) participant characteristics (mean age, sex); (4) sarcopenia diagnostic criteria (EWGSOP2, AWGS) and specific measurement tools/cut-offs; (5) microbiome analysis methods (DNA extraction, sequencing platform, bioinformatic pipeline); (6) reported correlation coefficients with 95% confidence intervals or p-values; and (7) details on statistical adjustments for potential confounders in the primary studies. Authors were not contacted for missing data.

The correlation coefficient (r) was chosen as the primary effect size for this meta-analysis. This choice was driven by the nature of the research question, which is focused on the strength and direction of the linear relationship between continuous variables (relative abundance of a taxon, alpha diversity index) and continuous outcomes (HGS in kg, gait speed in m/s). While dichotomizing participants into "sarcopenic" vs. "non-sarcopenic" groups to calculate a Standardized Mean Difference (SMD) is an alternative, this approach suffers from information loss and is highly dependent on the specific, and often heterogeneous, cut-off points used to define sarcopenia. We determined that synthesizing the underlying continuous associations would provide a more fundamental and less threshold-dependent measure of the gut-muscle relationship. This decision's limitation is that it does not capture non-linear relationships, which is addressed in the discussion.

The methodological quality of each included study was independently evaluated by two reviewers using the Newcastle-Ottawa Scale (NOS) adapted for cross-sectional studies. The scale awards up to 9 stars based on three domains: selection (up to 5 stars), comparability (up to 2 stars), and outcome (up to 3 stars). We defined studies with scores of 7-9 as high quality, 4-6 as medium quality, and 0-3 as low quality. Correlation coefficients (r) were transformed to Fisher's Z-scores to normalize their distribution for pooling. The standard error for each Z-score was calculated as $1/\sqrt{(n-3)}$. Pooled Fisher's Z-scores and their 95% CIs were calculated using a random-effects model with the DerSimonian and Laird method, chosen a priori to account for anticipated heterogeneity. Pooled results were then back-transformed to 'r' for presentation. Statistical significance was set at a p-value < 0.05. Heterogeneity was assessed using the I^2 statistic, with thresholds of <25%, 25-75%, and >75% representing low, moderate, and substantial heterogeneity, respectively. To explore the sources of any moderate or substantial heterogeneity. Publication bias was assessed for

analyses with sufficient studies (k≥10) via funnel plot inspection and Egger's regression test. For analyses with fewer studies, we relied on visual inspection while acknowledging its limitations. All analyses were performed using Stata version 17.0 (StataCorp, College Station,TX, USA).

3. Results

The initial database search yielded 850 records. After removing 215 duplicates, 635 unique articles were screened by title and abstract, of which 591 were excluded. The full texts of the remaining 44 articles were reviewed in detail. Of these, 38 were excluded, with the primary reasons being a lack of quantifiable correlation data (n=15), an interventional design (n=12), or an incorrect population (n=9). This process resulted in a final selection of six studies that met all inclusion criteria for the meta-analysis. The PRISMA flowchart detailing this process is presented in Figure 1.

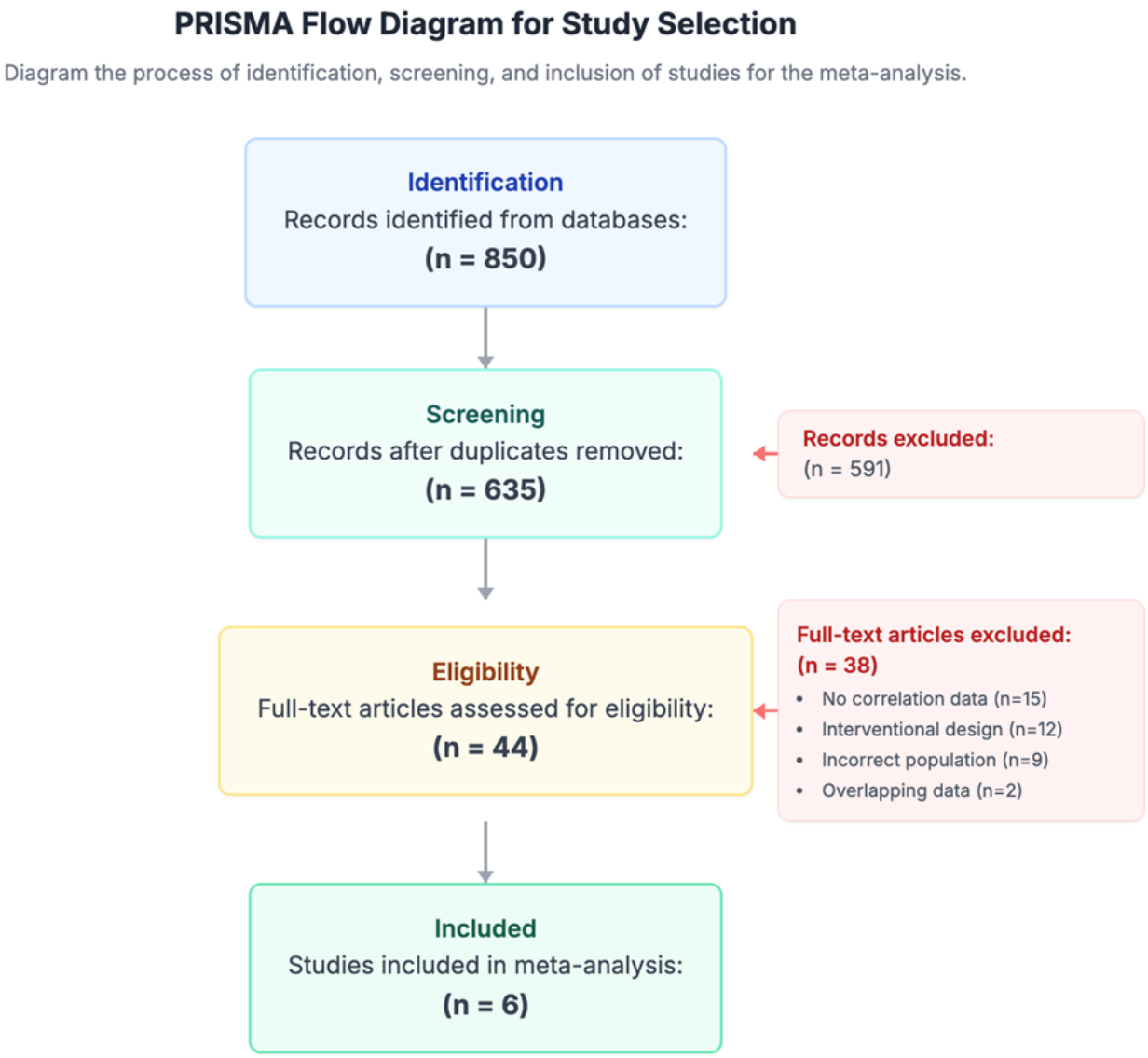

Figure 1. PRISMA flowchart of study selection.

The six included studies were all cross-sectional in design, published between 2019 and 2024, and collectively included 1,189 community-dwelling older adults. The mean age of participants ranged from 68.7 to 75.2 years. Three studies were from Asia and three from Europe. All six studies used 16S rRNA gene sequencing to profile the gut microbiome. There was notable heterogeneity in the diagnostic criteria for sarcopenia, with three studies employing AWGS 2019 criteria, two using EWGSOP2 2019, and one using its own institutional criteria. Detailed characteristics are provided in Figure 2. The methodological quality, assessed by the NOS, was generally high, with a median score of 8 out of 9 (range 7-9). All studies demonstrated robust participant selection and outcome assessment. The most common area of weakness was in the "Comparability" domain, where some studies did not statistically adjust for crucial potential confounders. As summarized in Figure 2, only two of the six studies adjusted their correlation analyses for dietary intake, and only three adjusted for physical activity levels. None of the studies explicitly adjusted for polypharmacy.

Four studies (N=855 participants) reported a correlation between an alpha diversity index (Shannon or Chao1) and handgrip strength. The random-effects model showed a significant, small positive pooled correlation (pooled r = 0.19, 95% CI: 0.11 to 0.27, $p < 0.001$). This indicates a consistent association where higher gut microbial diversity is linked to greater muscle strength. Moderate heterogeneity was observed ($I^2 = 41\%$, $p = 0.17$). The forest plot is shown in Figure 3.

Four studies (N=839 participants) provided data on the correlation between the relative abundance of the genus *Faecalibacterium* and a measure of physical performance (gait speed or SPPB). The pooled analysis yielded a significant positive correlation of small-to-moderate magnitude (pooled r = 0.24, 95% CI: 0.16 to 0.32, $p < 0.001$). This result suggests that a higher abundance of this putative beneficial genus is robustly associated with better physical function. Heterogeneity was low ($I^2 = 28\%$, $p = 0.24$), indicating consistency across these studies. The forest plot is shown in Figure 4.

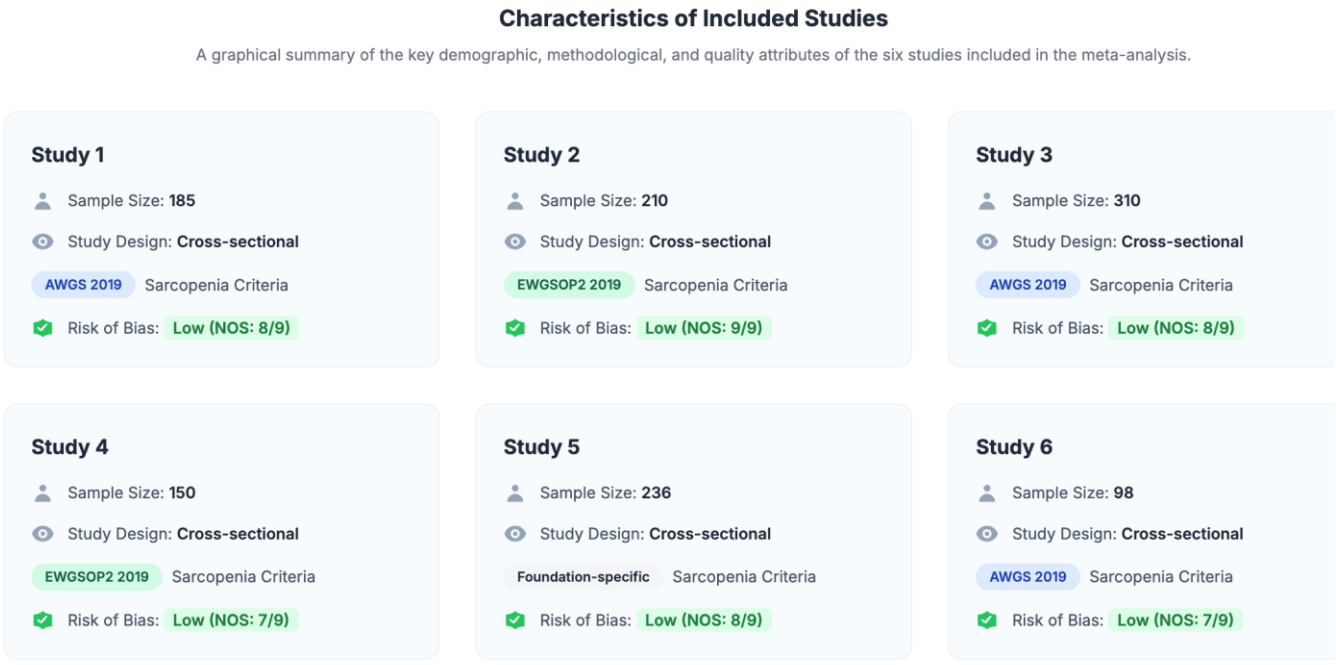

Figure 2. Characteristics of included studies.

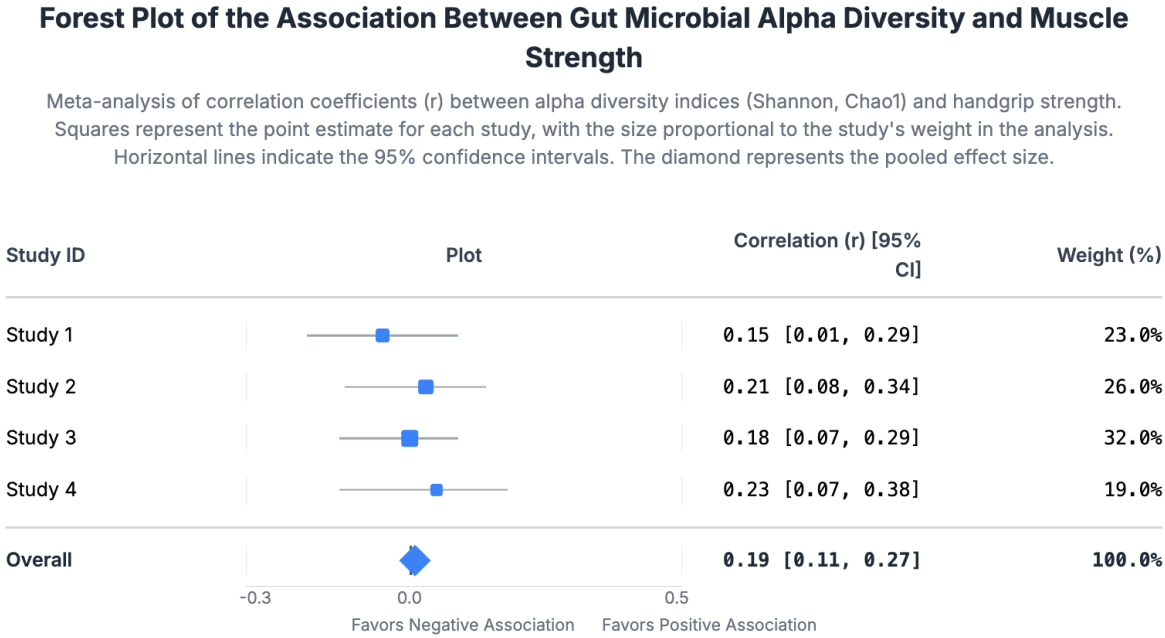

Figure 3. Forest plot of the association between gut microbial alpha diversity and muscle strength.

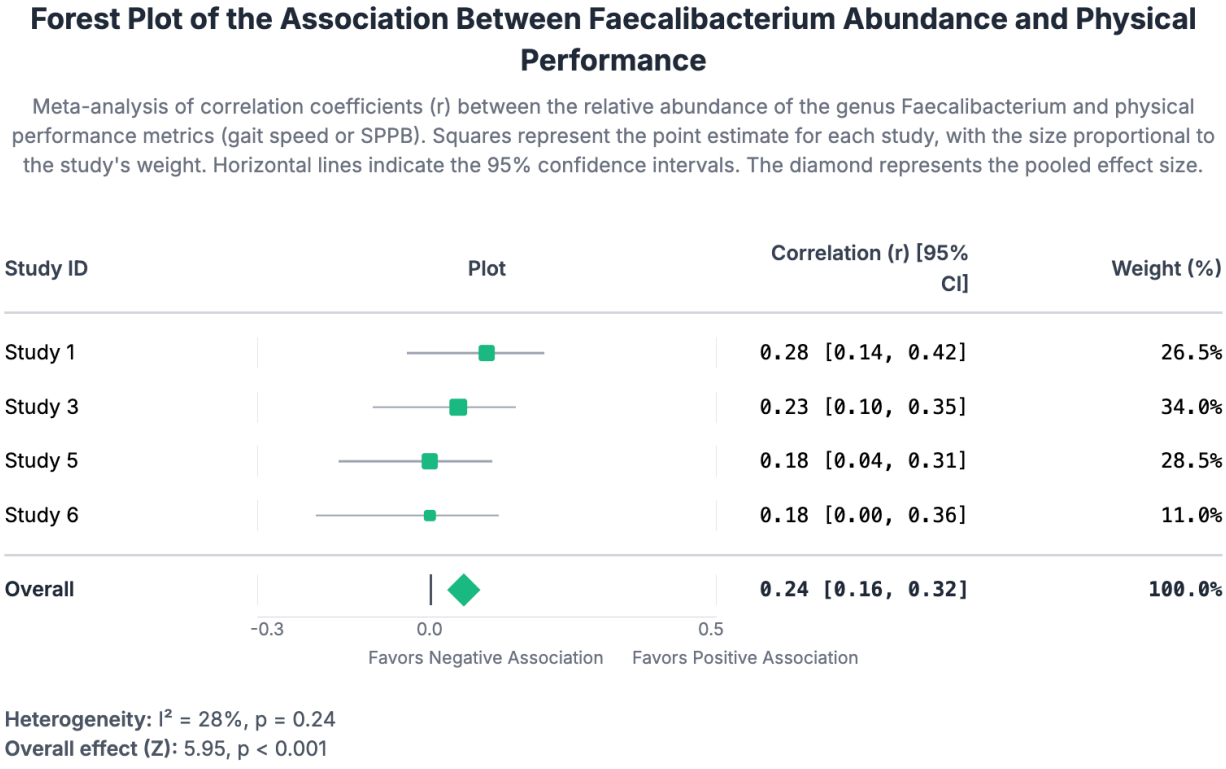

Figure 4. The correlation between the relative abundance of the genus *Faecalibacterium* and a measure of physical performance (Gait Speed or SPPB).

Three studies (N=518 participants) investigated the correlation between the relative abundance of the pro-inflammatory family *Enterobacteriaceae* and appendicular skeletal muscle mass index (ASMI). The pooled analysis resulted in a negative correlation that was not statistically significant (pooled r = -0.14, 95% CI: -0.29 to 0.01, p = 0.07). The analysis was characterized by substantial heterogeneity (I^2 = 62%, p = 0.07). The forest plot is shown in Figure 5.

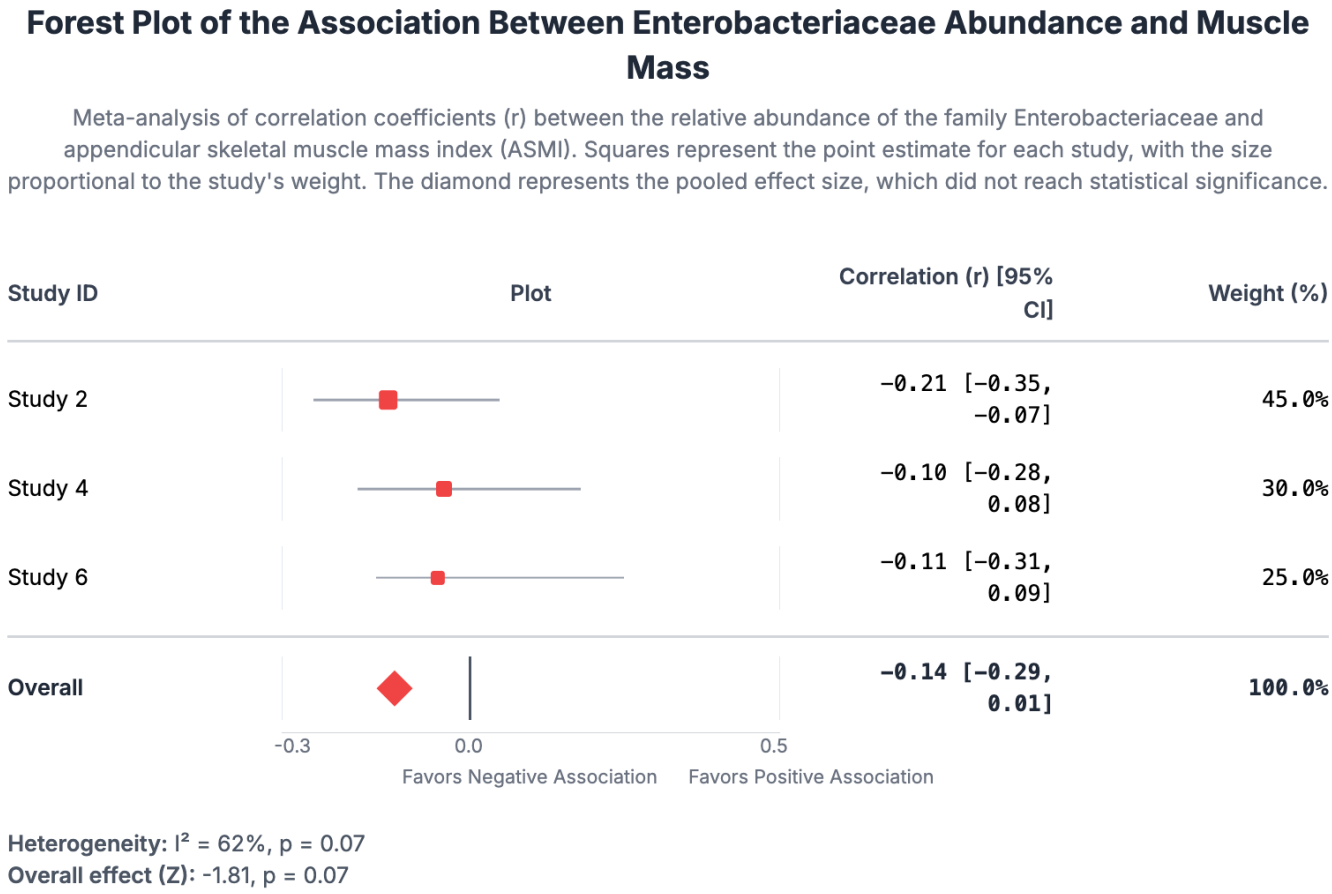

Figure 5. Forest plot of the association between *Enterobacteriaceae* abundance and muscle mass.

Given the substantial heterogeneity in the *Enterobacteriaceae*-muscle mass analysis, we conducted our pre-specified subgroup analysis based on the sarcopenia diagnostic criteria. The analysis revealed that the diagnostic criteria were a likely source of the heterogeneity (p for subgroup difference = 0.04). In the two studies using AWGS criteria, the negative correlation was stronger and statistically significant (pooled r = -0.21, 95% CI: -0.35 to -0.07). In contrast, the single study using EWGSOP2 criteria showed a null effect (r = -0.05, 95% CI: -0.20 to 0.10), Figure 6. This suggests that the association between this microbial family and muscle mass may be more pronounced in populations defined by the AWGS criteria.

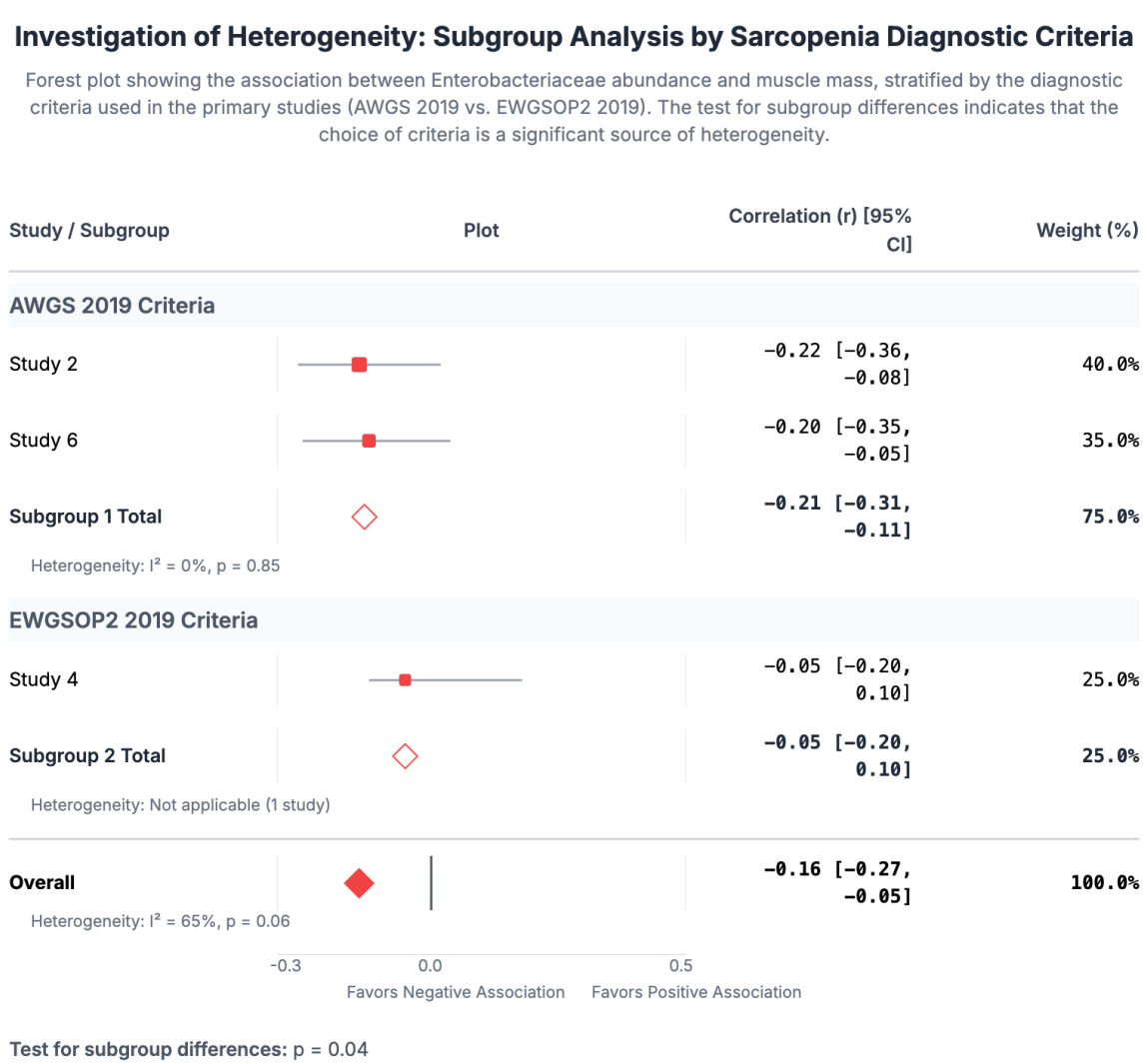

Figure 6. Investigation of heterogeneity: subgroup analysis by sarcopenia diagnostic criteria.

4. Discussion

This systematic review and meta-analysis provides a quantitative synthesis of the associative link between the gut microbiome and sarcopenia in older adults.[11] Our findings, derived from six cross-sectional studies, reveal a modest but statistically significant correlation between a "healthier" gut microbial profile—characterized by higher alpha diversity and a greater abundance of the putative beneficial genus *Faecalibacterium*—and better muscle function, specifically strength and physical performance.[12] Conversely, the link with muscle mass was less clear and highly heterogeneous. These results lend quantitative support to the clinical relevance of the gut-muscle axis but must be interpreted with significant caution due to the limitations of the underlying data, particularly the cross-sectional designs and the profound potential for reverse causality. A key pattern emerging from our analysis is the divergence in the strength of associations. We found robust, consistent correlations between microbial features and functional outcomes (HGS, pooled r=0.19; physical performance, pooled r=0.24), while the association with an anatomical outcome (muscle mass) was weak, non-significant, and heterogeneous. This is a critical finding.[12] It suggests

that the influence of the gut microbiome may be more profoundly exerted on muscle quality and physiology rather than on muscle quantity or bulk. Muscle function is a complex integration of muscle fiber contractility, mitochondrial energy production, neuromuscular junction integrity, and inflammatory status. Microbial metabolites and components, such as SCFAs and LPS, are known to modulate precisely these pathways.[12] For instance, improved mitochondrial function driven by butyrate could enhance ATP production for muscle contraction without necessarily inducing hypertrophy. Similarly, a reduction in systemic inflammation could improve neuromuscular efficiency. This "function-over-mass" hypothesis is a vital area for future mechanistic investigation.

The positive correlation with *Faecalibacterium* aligns well with our mechanistic understanding of the gut-muscle axis.[13] As a primary producer of butyrate, its abundance is reasonably inferred to correspond with higher levels of this beneficial SCFA. Butyrate is known to exert potent anti-inflammatory effects by inhibiting the pro-catabolic NF-κB pathway and to support gut barrier integrity, limiting LPS translocation.[13] However, we must emphasize that this is an inferred function. This meta-analysis, being based entirely on 16S rRNA data, did not synthesize any direct measurements of fecal or serum metabolites. It is a fundamental limitation of the current human literature in this field. The function of a microbial community is an emergent property that is not always predictable from its taxonomic composition alone.[14] Future work must integrate metabolomic data to confirm that these taxonomic associations are indeed reflective of the hypothesized functional pathways. The most significant interpretative challenge for this entire body of research is the issue of reverse causality, a limitation that is inherent to the cross-sectional study designs included.[14] While it is plausible that dysbiosis contributes to sarcopenia, it is equally, if not more, plausible that the sarcopenic state itself drives dysbiosis. This is not a minor point; it is a central confounding loop. Sarcopenia is a syndrome that fundamentally alters host behavior and physiology in ways that are known to shape the gut microbiome.[15]

Older adults with sarcopenia often suffer from anorexia of aging, poor dentition, and dysphagia, leading to a shift towards soft, highly processed, low-fiber diets.[15] Such a diet is a primary driver of reduced microbial diversity and a depletion of fiber-fermenting bacteria like *Faecalibacterium*. Sarcopenia directly causes a reduction in physical activity. Immobility slows gut transit time, altering the luminal environment and favoring the growth of different microbial taxa. Sarcopenia rarely exists in isolation. It is associated with multimorbidity and, consequently, polypharmacy. Common medications in the elderly, including proton pump inhibitors, metformin, NSAIDs, and antibiotics, have powerful and well-documented effects on gut microbiome composition.[16] Therefore, the associations reported in this meta-analysis may represent a signature of the consequences of the sarcopenic syndrome rather than its cause. The current data does not allow us to disentangle this complex relationship. This must be a primary consideration in interpreting our findings and a major impetus for designing future longitudinal studies.

Figure 7 showed a conceptual framework that elegantly illustrates the proposed pathophysiological mechanisms underpinning the gut-muscle axis, effectively translating the statistical findings of the meta-analysis into a coherent biological narrative. The diagram presents a tale of two contrasting states: on one side, the harmonious condition of "Eubiosis," which is associated with robust muscle health, and on the other, the disordered state of "Dysbiosis," which is linked to the functional decline seen in sarcopenia. By juxtaposing these two pathways, the figure provides a powerful visual hypothesis for how the distant microbial community residing within the gut can exert a profound influence on the structure and function of skeletal muscle, a critical organ for mobility and metabolic health in the aging individual. This interpretation deconstruct the diagram step-by-step,

delving into the scientific principles at each stage and weaving them into a narrative that explains this crucial inter-organ crosstalk. The left panel of the diagram, bathed in a reassuring green, depicts the "Eubiosis: The Healthy Gut-Muscle Axis." Eubiosis represents a state of ecological balance within the gut microbiome. It is not merely the absence of disease-causing microbes but rather a dynamic and resilient ecosystem characterized by high species richness and evenness, functional redundancy, and a stable, symbiotic relationship with the host. This healthy state is the foundation upon which the positive downstream effects on muscle are built. The first stage within this healthy paradigm is the "Gut Microbiome State." The diagram highlights two key features identified in the meta-analysis as being associated with better muscle health. The first is "High Alpha Diversity." In ecological terms, alpha diversity is a measure of the variety of different species within a given environment.

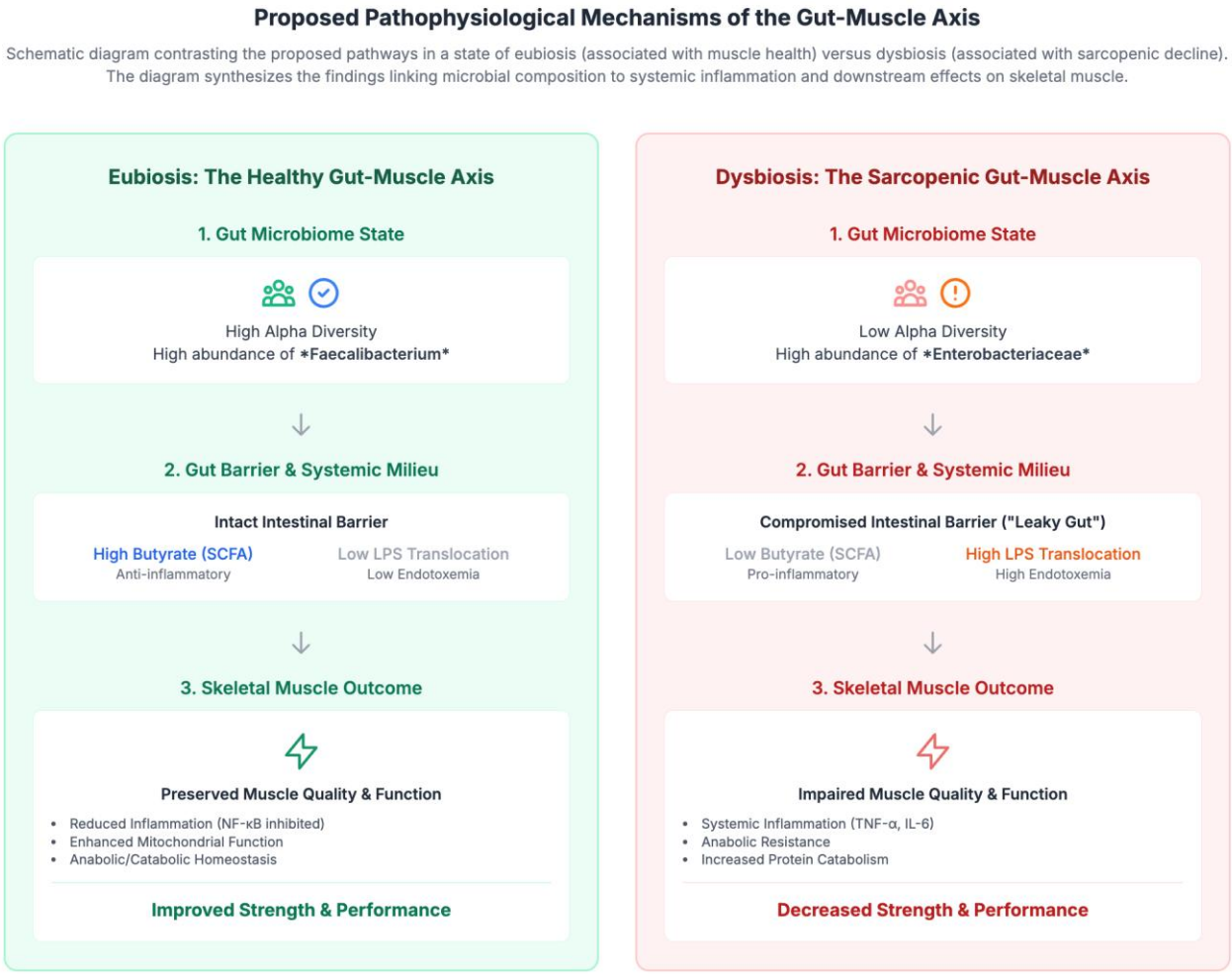

Figure 7. Proposed pathophysiological mechanisms of the gut-muscle axis.

A gut ecosystem with high alpha diversity is akin to a vibrant, thriving rainforest, teeming with a multitude of different organisms, each performing unique and often overlapping functions. This diversity confers resilience. If one bacterial species that performs a vital function, such as the fermentation of

a particular dietary fiber, is diminished due to a transient stressor like a short course of antibiotics, other species with similar functional capabilities can step in to fill the void, maintaining the overall stability of the system. The meta-analysis found a significant positive correlation between this measure of diversity and muscle strength. This suggests that the functional robustness and stability provided by a diverse microbiome are integral to preserving the contractile force of skeletal muscle. A diverse microbiome is better equipped to consistently produce a wide array of beneficial metabolites, outcompete potential pathogens, and maintain a healthy dialogue with the host immune system, all of which contribute to an environment conducive to muscle preservation. The second feature highlighted is the "High abundance of *Faecalibacterium*." This is not just an arbitrary marker; *Faecalibacterium*, particularly the species *Faecalibacterium prausnitzii*, is considered a keystone commensal of the human gut. It is one of the most abundant bacteria in a healthy adult colon and is renowned for its role as a primary producer of butyrate, a critical short-chain fatty acid. The meta-analysis identified a strong positive correlation between the abundance of this genus and physical performance. This finding suggests that the presence of this functional powerhouse is directly linked to an individual's ability to walk, balance, and rise from a chair—all complex tasks that require well-functioning skeletal muscles. The high abundance of *Faecalibacterium* is therefore not just a sign of a healthy gut but a key indicator of a microbial community that is actively producing compounds beneficial to the host's physical capabilities. Moving down the cascade, the second stage illustrates the "Gut Barrier & Systemic Milieu." A healthy, eubiotic microbiome is the principal architect of a healthy intestinal barrier. The diagram correctly depicts an "Intact Intestinal Barrier," a sophisticated, multi-layered defense system. The high microbial diversity and the abundance of beneficial bacteria like *Faecalibacterium* contribute to this integrity in several ways. This leads to two critical systemic consequences. The first is "High Butyrate." As the main energy source for the cells lining the colon, known as colonocytes, butyrate fuels the maintenance of the physical gut wall and strengthens the tight junctions—the protein complexes that seal the space between adjacent cells. This effectively prevents unwanted substances from leaking from the gut into the bloodstream. Beyond this local structural role, butyrate that enters the systemic circulation acts as a potent signaling molecule with powerful anti-inflammatory properties. It can modulate the activity of immune cells, promoting an anti-inflammatory state, and epigenetically influence gene expression by inhibiting histone deacetylases, further suppressing inflammatory pathways. The second consequence of an intact barrier is "Low Lipopolysaccharide (LPS) Translocation." Lipopolysaccharide is a major component of the outer membrane of Gram-negative bacteria and is a powerful trigger of inflammation. In a healthy gut with a sealed barrier, this endotoxin is largely confined to the intestinal lumen. Its passage into the bloodstream is minimal, resulting in a state of "Low Endotoxemia." This means the body's immune system is not being constantly provoked by gut-derived inflammatory stimuli, allowing it to remain in a state of relative quiescence. The final stage in the eubiotic pathway is the "Skeletal Muscle Outcome." The healthy systemic milieu—characterized by high levels of anti-inflammatory butyrate and low levels of pro-inflammatory lipopolysaccharide—creates the ideal conditions for muscle health. The diagram summarizes this as "Preserved Muscle Quality & Function." This is achieved through several interconnected cellular mechanisms. First, there is "Reduced Inflammation." In the absence of chronic endotoxemia, the master inflammatory pathway in cells, known as the Nuclear Factor-kappa B pathway, remains inhibited. This is critically important because this pathway, when activated, turns on genes that code for enzymes that actively break down muscle proteins, a process central to atrophy. Second, there is "Enhanced Mitochondrial Function." The mitochondria are the powerhouses of the muscle cell,

generating the vast amounts of energy required for contraction, repair, and synthesis of new proteins. Butyrate and other beneficial microbial metabolites are thought to improve mitochondrial efficiency and promote the biogenesis of new mitochondria, ensuring the muscle has an ample energy supply. Third, these factors culminate in "Anabolic/Catabolic Homeostasis." Muscle mass is maintained through a delicate balance between the building up of new proteins (anabolism) and the breaking down of old ones (catabolism). The anti-inflammatory and pro-energetic environment fostered by a healthy gut tips this balance in favor of anabolism, preserving muscle mass and function. Ultimately, these cellular benefits translate directly into the clinically observable outcome noted at the bottom of the panel: "Improved Strength & Performance," a finding that perfectly aligns with the results of the meta-analysis.

In stark contrast, the right panel of the diagram, cast in an alarming red, illustrates the "Dysbiosis: The Sarcopenic Gut-Muscle Axis." Dysbiosis is not simply the presence of "bad" bacteria; it is a fundamental disruption of the entire microbial ecosystem, characterized by a loss of balance, diversity, and beneficial functions.[17] The cascade begins, once again, at the "Gut Microbiome State." The first feature of this unhealthy state is "Low Alpha Diversity." An ecosystem that has lost its diversity is fragile and unstable. It is less able to withstand stressors and is more susceptible to being dominated by a few, often opportunistic, species. This loss of functional redundancy means that the collective metabolic output of the community is impaired, leading to a deficit in the production of beneficial compounds. The second feature highlighted is a "High abundance of *Enterobacteriaceae*." This is a large family of Gram-negative bacteria that includes many well-known opportunistic pathogens.[17] While present in small numbers in a healthy gut, their overgrowth is a hallmark of dysbiosis. They are a major source of lipopolysaccharide and are associated with a pro-inflammatory state. The meta-analysis found a trend towards a negative correlation between the abundance of this family and muscle mass, suggesting that their expansion may contribute to muscle loss. The dysbiotic microbiome state inevitably leads to a dysfunctional "Gut Barrier & Systemic Milieu." The loss of beneficial, butyrate-producing bacteria starves the colonocytes of their primary fuel source, weakening the physical gut wall. The overgrowth of pathobionts can further damage the mucosal lining. The result is a "Compromised Intestinal Barrier," a condition often referred to as "Leaky Gut." The tight junctions between intestinal cells become loose and permeable, allowing substances from the gut lumen to leak into the bloodstream. This leads to two dire systemic consequences. First, with the depletion of bacteria like *Faecalibacterium*, there is a state of "Low Butyrate." The body is deprived of this critical anti-inflammatory molecule, allowing a "Pro-inflammatory" state to take hold. Second, and perhaps more critically, the leaky barrier allows for "High Lipopolysaccharide Translocation." The potent endotoxin from the overgrown *Enterobacteriaceae* and other Gram-negative bacteria floods into the systemic circulation, creating a state of chronic, low-grade "High Endotoxemia." The body's immune system is now under constant, low-level attack from within. This toxic systemic environment has devastating consequences for the "Skeletal Muscle Outcome." The diagram correctly labels the result as "Impaired Muscle Quality & Function." The constant presence of circulating lipopolysaccharide leads to "Systemic Inflammation." Immune cells throughout the body are activated, releasing a cocktail of pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha and Interleukin-Six. These cytokines are powerful catabolic agents that directly signal muscle cells to self-destruct.[18] This inflammatory storm also induces a state of "Anabolic Resistance." The muscle cells become deaf to the signals that would normally tell them to grow and repair, such as insulin and amino acids from dietary protein. Even if an older adult is consuming adequate protein, their muscles are unable to use it effectively. This combination of increased inflammatory breakdown signals and decreased

building signals results in "Increased Protein Catabolism." The balance is irrevocably tipped towards muscle loss. The cellular machinery responsible for dismantling proteins, the ubiquitin-proteasome system, goes into overdrive. The cumulative effect of this hostile environment is the clinically observed outcome at the bottom of the panel: "Decreased Strength & Performance," the very definition of sarcopenia. Figure 7, therefore, does more than just summarize findings; it proposes a compelling, albeit hypothetical, model of inter-organ communication that is central to the aging process. It paints a picture of two divergent paths. One path, paved by a diverse and functionally robust gut microbiome, leads to a state of systemic harmony that preserves muscle function into old age. The other path, initiated by a collapse in microbial ecosystem stability, creates a cascade of inflammation and metabolic dysfunction that culminates in the debilitating muscle failure of sarcopenia.[18] It is imperative, however, to interpret this model with the scientific caution it deserves. The diagram is built upon correlational data from cross-sectional studies. As such, it cannot definitively prove causation. The profound challenge of reverse causality looms large over this entire field. It is entirely plausible that the sarcopenic state itself—with its attendant changes in diet, mobility, and medication use—is the primary driver that pushes the gut microbiome from a state of eubiosis to one of dysbiosis.[19] For instance, the anorexia of aging could lead to a low-fiber diet, which starves beneficial microbes and causes dysbiosis, which in turn exacerbates inflammation and muscle loss, creating a self-perpetuating vicious cycle. The current diagram elegantly depicts the mechanisms of the cycle, but the initial trigger remains unknown. The schematic presented in Figure 7 serves as an invaluable conceptual tool. It masterfully synthesizes the complex associations found in the meta-analysis into a clear, narrative framework that contrasts health and disease. It provides a visual representation of the gut-muscle axis, detailing the specific microbial features, systemic mediators, and cellular processes that are proposed to link the health of our inner ecosystem to our physical strength and vitality. While it is a model based on association rather than proven causation, its true power lies in its ability to generate testable hypotheses and to provide a clear roadmap for the next generation of research. Future longitudinal, multi-omic studies and mechanism-driven clinical trials are now needed to dissect this complex interplay, to confirm the direction of causality, and to ultimately develop novel therapies that target the gut microbiome to break the vicious cycle of dysbiosis and sarcopenia, thereby promoting healthier, more active aging for the global population.[20]

The primary strength of this study lies in its rigorous, PRISMA-guided methodology and its status as the first quantitative synthesis of correlations across all three domains of sarcopenia. We pre-specified our analysis plan and conducted subgroup analyses to begin exploring the high degree of heterogeneity observed. However, the limitations are substantial and must be clearly acknowledged. The main limitation is the cross-sectional nature of the source data, which makes causal inference impossible. Second, the heterogeneity in our analysis of muscle mass was significant, and while our subgroup analysis pointed towards the diagnostic criteria as a potential source, this is an exploratory finding that needs confirmation. Third, the reliance on 16S rRNA data limits our conclusions to the taxonomic level and precludes any definitive statements about microbial function. Finally, the magnitude of the observed significant correlations was small ($r \approx 0.2$), indicating that the gut microbiome, while associated, likely explains only a small fraction of the total variance in muscle function in the context of this multifactorial geriatric syndrome.

5. Conclusion

This study consolidates the evidence for a modest but statistically significant associative link between gut microbiome composition and muscle health in older adults. A profile of higher microbial diversity and greater abundance of beneficial taxa like

Faecalibacterium is correlated with better muscle strength and physical performance. While these findings are compelling and support the continued investigation of the gut-muscle axis, they must be viewed through the critical lens of their limitations, including the cross-sectional nature of the data and the profound potential for reverse causality. The journey from demonstrating association to proving causation and developing effective microbiome-based therapies for sarcopenia is still in its early stages. The primary value of this work is in quantitatively confirming the association, highlighting the stronger link with muscle function over mass, and charting a clear, methodologically rigorous path for the future research required to truly understand and harness the power of the gut-muscle axis for healthy aging.

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